Chronic Ischemic Heart Disease Pharmacology

Introduction

The treatment of chronic coronary artery disease focuses on two main goals: reducing myocardial demand to improve the demand/supply mismatch and preventing plaque rupture and thrombosis. This lesson is intended to be attempted only after CAD #1–3 and assumes an understanding of atherosclerosis and the concepts of demand vs. supply ischemia.

The treatment of chronic ischemic heart disease, coronary artery disease, atherosclerosis of the coronary vessels, or any of their synonyms involves preventing the rupture and thrombosis of a plaque and reducing the work of the heart. The same treatment is recommended for patients with coronary artery disease, whether their plaque is surgically corrected (stent or CABG, the final cardiac lesson) or not—medical management only. The treatment is to prevent acute coronary syndrome, reduce the risk of rupture and thrombosis (statins and antiplatelets), decrease the overall work of the heart, and prevent neurohormonal remodeling of the ventricles, just as we saw in heart failure. The combination of β-blockers and ACE/ARBs satisfies both work reduction and the prevention of neurohormonal remodeling, just as we saw in heart failure. Unlike heart failure, coronary artery disease is less impacted by volume, so diuretics play no role in coronary vascular disease. Instead, certain medications can provide blood pressure control and anginal symptom relief. After maximizing the ACE/ARB and β-blocker, anti-anginals are added to provide symptom relief.

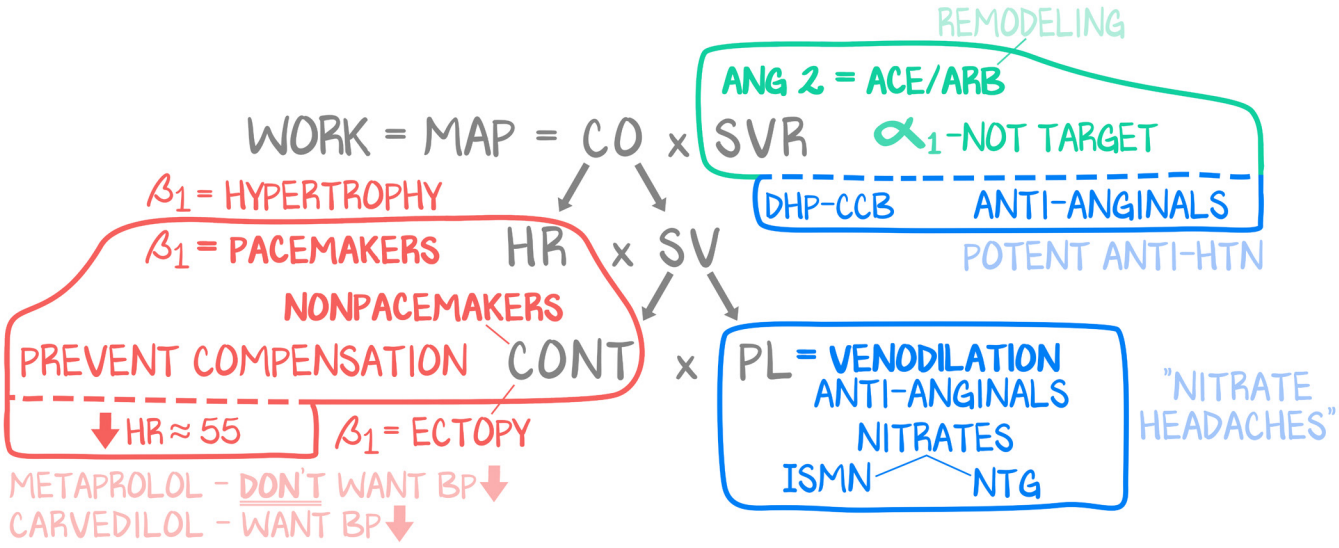

Figure 4.1: MAP Equation
The ~~MAP~~ work equation provides a method to catalog the treatment of coronary artery disease. It is organized a little differently than usual. This time, anything that is blue is an anti-anginal, not a preload reducer. The mainstay is β-blockade to reduce the heart rate, limiting the "multiplier" of myocardial work per minute, and ACE/ARBs not only because they are afterload (and therefore work) reducers but also because of their synergistic effects with β-blockers to prevent ventricular remodeling. Max out the β-blocker and the ACE/ARB before adding anti-anginal (symptom relief) medications that affect blood pressure (e.g., nitrates, dihydropyridine calcium-channel blockers).

Every patient with coronary artery disease should be on AspirinStatinBetaBlockerACEInhibitor+DAPT.

That is all one word, with the + sounded out ("plus") and DAPT, an acronym, sounded out as if it were a word ("dapped," rhymes with rapped). Unless there is a really good reason that the patient cannot be on all five medications, they should be on all five medications. This lesson explores the physiological rationale behind why and discusses some empirical data.

RUPTURE/THROMBOSIS	WORK OF THE HEART
Antiplatelets reduce the risk of arterial thrombosis (DAPT = Aspirin, ADP $P2Y_{12}$ receptor antagonists	β-blockers reduce heart rate . . . and contractility, synergy with ACE/ARBs
Statins lower LDL cholesterol, preventing the progression of atherosclerosis	ACE inhibitors prevent remodeling . . . and reduce afterload, synergy with β-blockers
	Nitrates reduce preload

Table 4.1: Targets for Coronary Artery Disease

β-Blockers Reduce Oxygen Demand by Lowering Heart Rate and Reducing Contractility

You saw this information presented in almost the same way in the lesson on hypertension. There, we said that β-blockers are not used to treat hypertension. In CHF, we showed you how β-blockers reduce the hypertrophic signal to avoid both eccentric and concentric hypertrophy. In arrhythmia, β-blockers slow the heart rate. In acute coronary syndrome, they serve yet another purpose. Here, in chronic ischemic heart disease management, the main effect is to reduce the heart rate to reduce the overall work per minute of the heart. β-Blockers also prevent neurohormonal remodeling, amplify the effects of ACE/ARBs, and mitigate the risk of arrhythmia due to subclinical infarcts (mild ischemia that doesn't provoke pain but can set off a temporarily ischemic tissue). The goal is to reduce the heart rate to 55 bpm at rest.

Nonselective β-blockers block both β_1 and β_2, but they do not affect α_1. These blockers had no business treating hypertension, heart failure, rapid ventricular rates, and therefore are **NOT used in heart disease**. They are used for esophageal variceal hemorrhage in decompensated cirrhotics and can be used off-label for stage fright. They cause terrible depression, erectile dysfunction, and bradycardia and are the **only** β-blockers that induce **bronchoconstriction**, inducing asthma or COPD exacerbation. The nonselective β-blockers end in "-olol" and start with the letters in the back half of the alphabet—propranolol, nadolol, and timolol. Timolol eye drops are used in glaucoma.

Cardioselective β-blockers only block the β receptor on the heart, β_1. They do not block β_2, and they do not block α_1. β_1 Blockade means we benefit from negative chronotropy and negative inotropy, so reduced oxygen demand, without the side effects of β_2 blockade, would increase afterload. But because they don't block α_1, they don't drop the blood pressure, either. Cardioselective β-blockers are best used for **rate control** or when cardioprotection is needed from β_1 blockade, but the blood pressure is already low. They end in "-olol" and start with letters in the front half of the alphabet—atenolol, esmolol, and metoprolol. **Esmolol** is given as an **infusion** to control heart rate in aortic dissection. Oral **metoprolol** is used in heart failure, coronary artery disease, and atrial fibrillation. IV preparations can be used to slow tachyarrhythmias, like AFib with rapid ventricular response. Metoprolol tartrate must be given twice per day. Metoprolol succinate is the extended-release formulation, given once daily. Atenolol is not really used anymore since the advent of more modern, better-studied β-blockers (like metoprolol)

α And β antagonists block α_1 and β_1. That means negative chronotropy (β_1) and negative inotropy (β_1), as seen with cardioselective β-blockers, and reduced afterload (α_1). **Carvedilol** can be used for the treatment of coronary artery disease and heart failure with reduced ejection fraction (HFrEF). It is chosen over metoprolol when blood pressure reduction is desired. Other α_1-β_1-blockers are not used to treat coronary artery disease. This class can be recognized as ending in -alol or -ilol. **Labetalol** is used for hypertension, **not coronary artery disease**. Carvedilol is chosen when blood pressure control is also desired, and metoprolol is chosen when minimal change in blood pressure is desired.

DRUG	CLASS	INDICATION
Propranolol, nadolol	Nonselective (β_1, β_2)	Esophageal varices
Metoprolol	Cardioselective (β_1)	CAD, CHF, rate control
Carvedilol	α_1, β_1	CAD, CHF, BP control
Labetalol	α_1, β_1	BP Control

NONSELECTIVE β-BLOCKERS	CARDIOSELECTIVE β-BLOCKERS	HTN β-BLOCKERS
β_1 and β_2	β_1 only	β_1, β_2, and α_1
-olol suffix, second half of alphabet	-olol suffix, first half of the alphabet	-ilol, -elol
Propranolol, nadolol, timolol	Metoprolol, esmolol	Carvedilol, labetalol
Provoke bronchoconstriction Erectile dysfunction Depression	Bradycardia	Hypotension

Table 4.2: Synopsis of β-Blockers

ACE Inhibitors Reduce Oxygen Demand by Reducing Afterload

ACE-inhibitor mechanisms are discussed in detail in Hemodynamics #6: *Hypertension Pharmacology* and also in both the Renal and Endocrine modules. For our purposes here, we highlight the key features as they relate to cardiovascular disease.

Angiotensin 2 (Ang 2) is the perpetrator molecule of the renin-angiotensin-aldosterone system (RAAS) and has several effects. Angiotensin "tenses the angios" and induces vasoconstriction. This is separate from autonomic α stimulation. Ang 2 causes **arteriolar vasoconstriction**, causing an increase in afterload and increasing the work of the heart. Ang 2 also induces aldosterone expression from the adrenal gland, resulting in the reabsorption of sodium from the renal tubules and, therefore, reabsorption of water. The long-term consequence of this mechanism is an **increase in preload**. Increases in preload can lead to an increased end-diastolic volume, which means a stronger contraction, but more work for the heart. These patients are not volume overloaded like in HFrEF, so diuresis and aldosterone antagonism are not necessary. Blocking these effects would indeed reduce the workload of the heart, both more immediately (vasodilation) and over a longer course (reduced preload).

Empirical data has shown that the use of **ACE inhibitors** in the first 24 hours of an acute myocardial infarction had significantly better outcomes in ventricular function and mortality. Over time, ACE inhibitors showed preservation of ventricular function in long-standing ischemic heart disease—**prevention of ventricular remodeling**. Regardless, the benefits of preload reduction and afterload reduction are good, but the effects of preventing ventricular remodeling are better.

Angiotensin-converting enzyme (ACE) is found in the lungs, and it converts Ang 1 to Ang 2. ACE inhibitors prevent the conversion to active Ang 2. The problem is that ACE also prevents the metabolism of **bradykinin**. Bradykinin accumulation is responsible for the **dry cough** that ACE inhibitors can induce and **angioedema**. Angioedema is the swelling of blood vessels. When it happens

in the mouth or trachea, it can occlude the airway. If a patient gets angioedema while taking an ACE inhibitor, never give them an ACE inhibitor again, but immediately start them on an ARB (after the angioedema resolves).

ACE inhibitors end in the suffix "-pril," as in lisinopril, enalapril, and captopril.

Angiotensin receptor blockers (ARBs) end in the suffix "-artan," as in losartan, valsartan, and candesartan. They block Ang 2 from binding to its receptor, with all the same benefits of an ACE inhibitor—reduced afterload and preload and prevention of ventricular remodeling. Because ACE is left unopposed by an ARB, ACE can degrade bradykinin, meaning ARBs do **not cause cough or angioedema**. If a patient needs an ACE-i, but gets angioedema on an ACE-i, switch them to an ARB.

ACE/ARBs cause vasodilation of the efferent arteriole, reducing glomerular pressures and leading to a slight decrease in glomerular filtration rate (GFR). Expect a creatinine rise of 10% in 2 weeks. Both also prevent aldosterone release, which decreases ENaC channels in the collecting duct, which normally reabsorb sodium and excrete potassium. Blocking these channels' effects can result in **hyperkalemia**. Both classes are **teratogenic** and should be avoided in pregnancy or women who are trying to conceive. Being a woman of childbearing age is not an absolute contraindication to ACE/ARBs, but each patient's risk-benefit ratio must be individually assessed.

	ACE INHIBITORS	ANGIOTENSIN RECEPTOR BLOCKERS
Suffix	-pril	-sartan
Examples	Lisinopril, enalapril, captopril	Losartan, valsartan, candesartan
Bradykinin	Bradykinin disinhibition = dry cough, angioedema	No bradykinin disinhibition = no cough, no angioedema
Aldosterone	Aldosterone inhibition = hyperkalemia	Aldosterone inhibition = hyperkalemia
GFR	Ang 2 at efferent arteriole = 10% reduction in GFR	Ang 2 at efferent arteriole = 10% reduction in GFR
Pregnancy	Teratogenic	Teratogenic

Table 4.3: ACE/ARB
Summary table comparing the two classes, highlighting their similarities except for their effects on the bradykinin pathway.

Antiplatelets Reduce the Risk of Thrombosis

Plaque rupture exposes the thrombogenic lipid core to the bloodstream, and a fibrin thrombus forms. Primary hemostasis, the formation of a platelet plug, is required to form that fibrin clot. Platelet plug formation involves platelet adhesion to the vessel wall, activation of platelets, and aggregation of those activated platelets. Platelet activation is mediated by thromboxane-A_2 receptors and ADP receptor subtype $P2Y_{12}$—what we at OME always call the ADP-$P2Y_{12}$ receptor (a lot more on this in Heme/Onc).

Aspirin blocks COX-1 and COX-2 of the arachidonic acid pathway, leading to the downstream effect of reduced thromboxane A_2 (TXA_2) in platelet granules. Platelets release TXA_2 when already adhered to a site of endothelial injury. The binding of TXA_2 to its receptors on platelets that are passing by activates those incoming platelets, which helps form the platelet plug. Aspirin **irreversibly inhibits** these COX enzymes. The life span of a platelet is about 8 days, so one course of aspirin lasts about 7 days. The side effect of aspirin is **bleeding**, by the same mechanism as the desired effect—reduced platelet clot formation. Aspirin 81 mg is the mainstay of primary prophylaxis (pre-infarct, to prevent the first

one) as well as secondary prophylaxis (post-infarct, to prevent the next one) for coronary artery disease. For acute management of myocardial infarction, a single dose of 325 mg is administered. For chronic management, 325 mg causes more bleeding and does not prevent more thrombosis. 325 mg is for acute, 81 mg is for chronic.

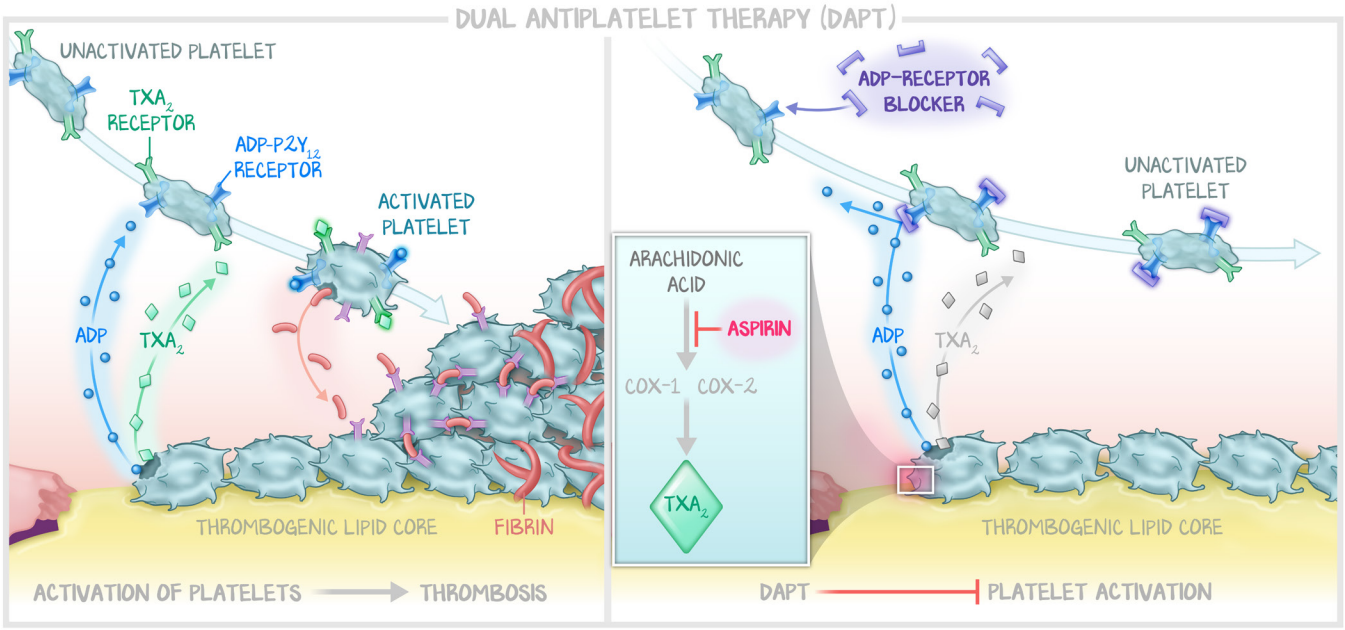

Figure 4.2: Antiplatelets
Both TXA_2 and ADP are released by platelets already adherent to a site of endothelial disruption. In this case, not only a site of endothelial damage but a site of exposed necrotic lipid core. TXA_2 and ADP receptor activation activates platelets. Activated platelets connect via fibrinogen, the substrate for the more stable thrombus—rupture and thrombosis. Aspirin blocks COX enzymes, preventing the production of TXA_2. ADP-$P2Y_{12}$ receptor antagonists bind to the ADP receptor, blocking the ADP from activating it. Both help prevent the inactivated platelets from being activated. This reduces not only the risk for thrombosis of a plaque but also the ability to clot everywhere else; therefore, a side effect of these medications is bleeding.

ADP-$P2Y_{12}$ receptor antagonists (or more simply ADP receptor blockers) are another form of antiplatelet commonly used in coronary artery disease. These do not have a common nomenclature, so you can be slipped one that you may miss. Names to recognize are **clopidogrel** (and its cousin prasugrel), **ticagrelor** (and its cousin cangrelor), and **ticlopidine**. They bind to and irreversibly inhibit the ADP receptor, which also causes platelet activation. If aspirin cannot be tolerated (COX-1 and COX-2 also make prostaglandins, prostaglandins protect the stomach; therefore, aspirin can cause gastritis), then these medications can be used instead. They also cause bleeding as a side effect. The chronic dose of clopidogrel is 75 mg. During acute management of myocardial infarction, a 300-mg loading dose is given. The similarities in dosing help us remember the difference between acute and chronic management—ASA 81, 325; clopidogrel 75, 300.

For those patients who receive a stent, **dual antiplatelet therapy** with an ADP-$P2Y_{12}$ receptor antagonist and aspirin is **mandatory** for a month (bare-metal stent) or a year (drug-eluting stent). Previous recommendations included discontinuation of dual antiplatelet therapy after the minimum duration to reduce bleeding risk. New guidelines call for lifelong dual antiplatelet therapy in **any patient with coronary artery disease** regardless of stent status, unless morbidity of bleeding warrants discontinuation.

Statins Reduce LDL Cholesterol, Reducing Atherosclerotic Plaques

Cholesterol metabolism is discussed in detail in Biochemistry Metabolism #14: *Triglyceride Mobilization*, and lipid-lowering agents in general were discussed in CAD #2: *Pharmacology of Atherosclerosis*. We withheld the details of statin therapy, only stating that they were, hands-down, the best drug class for the treatment of atherosclerosis. Here we explore the mechanism and clinical implications of their widespread use.

The liver can either use cholesterol from the diet (via chylomicrons), build new cholesterol, or take LDL out of the circulation via LDL receptors. Removing either the dietary source or the ability to make new cholesterol increases LDL receptor activity and pulls more LDL out of circulation so that it doesn't deposit into atheromas. The liver synthesizes cholesterol, and **HMG-CoA reductase is the enzyme for the rate-limiting step**. Statins are **HMG-CoA reductase inhibitors**.

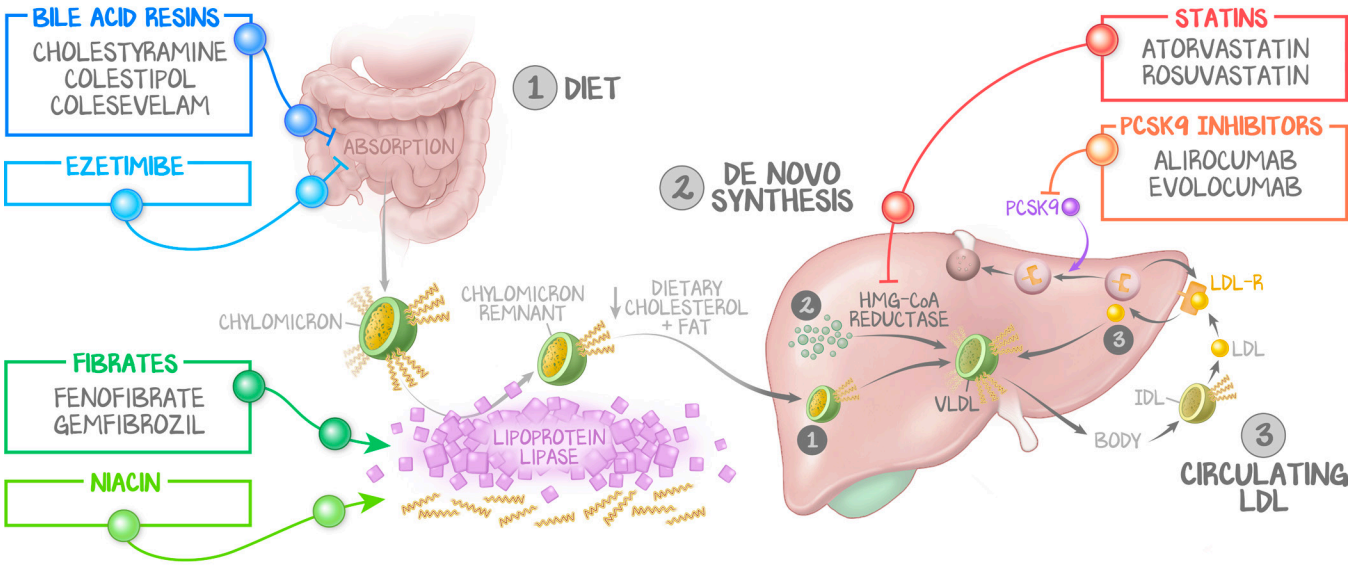

Figure 4.3: Effect of Statins
This is the same illustration you saw in CAD #2: *Pharmacology of Atherosclerosis*. Now, we focus on (3) circulating LDL. It is used here as a reminder of what works (statins, PCSK9 inhibitors), what could work (bile acid resins, ezetimibe), and what doesn't work at all (fibrates and niacin) in the management of atherosclerosis.

The liver has a quota of VLDL to make. It needs cholesterol to make it. Statins block the liver's synthesis of cholesterol. The only way the liver is going to meet its quota of VLDL is to take the LDL from the bloodstream. To do that, it must **upregulate the expression of LDL receptors on hepatocytes**. The benefit is not that less cholesterol is made, or that less cholesterol is circulating, or even that less VLDL particles are released into the bloodstream. The **benefit is that the LDL particles are removed from circulation**. VLDL production remains the same. Cholesterol circulation stays the same. The excess LDL causes disease. Statins remove the excess LDL, preventing atherosclerosis.

The goal is to get the patient on the maximum dose of a **high-potency statin**. Statins have the suffix "-statin," such as **atorvastatin** and **rosuvastatin**. Atorvastatin 80 mg and rosuvastatin 40 mg are high-potency statins. Lower doses or alternative statins (simvastatin, pravastatin, lovastatin) are not considered high-potency.

Because they directly affect hepatocytes, statins can induce **hepatoxicity**. Prior to initiating a statin, baseline liver function tests should be done, and LDL cholesterol assessed. There was formerly a recommendation that routine screening was appropriate to assess LDL cholesterol levels, liver function tests, and creatine kinase levels. Routine follow-up screening is **no longer considered appropriate**. Asymptomatic screening is not necessary, although jaundice should prompt a reassessment of the liver function tests. Statins can also induce **statin myopathy**, which results in painful weakness, diagnosed by elevated creatine kinase (CK) levels. The degree of hepatotoxicity induced by statins has minimal impact on AST and ALT levels—statin hepatotoxicity does not cause fulminant hepatic failure. However, being on a statin and suffering another acute hepatic insult worsens the result of that insult and increases the risk of fulminant hepatic failure. The degree of myopathy is likewise mild—statin myopathy does not cause rhabdomyolysis and renal failure. There must also be a significant amount of activity. Reducing the activity or pausing the statin will enable the myopathy to resolve. If hepatotoxicity or myopathy develops, temporarily discontinue the statin until symptoms resolve, then reinitiate the statin at a lower dose or with a lower potency statin.

The goal is to get the LDL cholesterol down, but there is **no target number**. LDL levels are part of the decision-making as to whether to initiate a patient on a statin who does not already have atherosclerotic disease but does have risk factors. When it is decided that the patient needs a statin (all patients with coronary artery disease are started on a statin), the goal is to get that patient on a statin at the highest potency and at the highest dose the patient can tolerate.

Anti-Anginals Are Adjuncts

Nitrates are prodrugs of nitric oxide. Nitric oxide is normally made by endothelial cells from L-arginine in the tunica intima. The nitric oxide crosses into the smooth muscle cells of the tunica media. There, nitric oxide stimulates guanylyl cyclase (GC). GC converts GTP to cGMP. cGMP is synonymous with dilation (a statement you will see elsewhere in the course). The downstream effect of this is tunica media smooth muscle relaxation of arterioles—**vasodilation**. The benefit of nitrates comes from **venodilation**, which increases venous pooling, reducing preload. This reduced preload delivers a smaller end-diastolic volume, and therefore a smaller workload of the heart.

Nitroglycerin is a rapid-acting sublingual or transdermal preparation. When a patient experiences angina, they are instructed to take nitroglycerin.

Isosorbide mononitrate is a long-acting preparation that can be used as an antihypertensive to bring anginal relief. Side effects of nitrates are **headache** ("nitro headaches" are common in patients on nitro who didn't have an MI) and hypotension.

There is a black-box warning for nitrates and PDE-5 inhibitors, such as **sildenafil** and **tadalafil**. Nitrates stimulate the production of cGMP. PDE-5 inhibitors reduce the degradation of cGMP. Hitting this system from both ends creates a critical drop in venous return, resulting in **hypotension**.

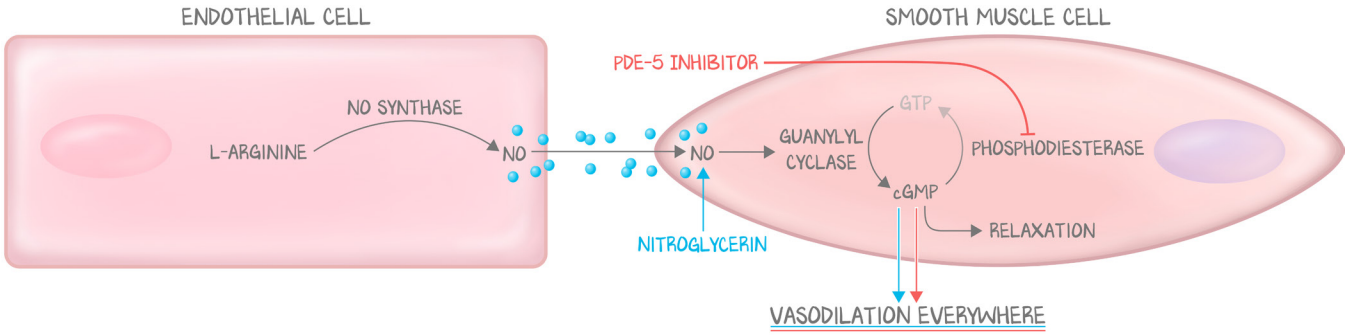

Figure 4.4: Nitrates
In response to various stimuli (including parasympathetic innervation of endothelial cells), endothelial cells turn L-arginine into nitric oxide (NO). Nitric oxide diffuses to vascular smooth muscle cells, where it stimulates guanylyl cyclase. Guanylyl cyclase converts GTP into cGMP. The mechanism by which cGMP induces the relaxation of smooth muscle is covered in General Physiology #15: *Smooth Muscle* but isn't needed to understand this figure. Anywhere cGMP is in smooth muscle, throughout the body, assume it means relaxation. For patients taking a PDE-5 inhibitor for erectile dysfunction, more cGMP means more penile artery dilation and an erection. But the drug is not specific to the penile arteries but rather the endothelium of all blood vessels. Nitrates become nitric oxide and exert their effects through that manner. With the addition of nitroglycerin (or vice versa, a patient is on a long-acting nitrate and takes a PDE-5-inhibitor), there is both a stimulator and an inhibitor of the signal, leading to an unsafe drop in blood pressure.

Other Anti-Anginals

Dihydropyridine calcium-channel blockers (amlodipine, nifedipine) are also used as antihypertensives and anti-anginals. Non-dihydropyridine calcium-channel blockers (diltiazem, verapamil) are used for rate control and do not contribute to anti-angina, blood pressure control, or coronary artery disease management.

Ranolazine is a chest pain reducer. It blocks late inward Na^+ currents in cardiac myocytes, thereby decreasing calcium accumulation. Less calcium, less force of contraction, less work of the heart. It is a last resort medication, often used in known vascular disease that is not amenable to stenting or CABG. It serves only to **relieve symptoms**.

NITRATES	CCB	RANOLAZINE
Venodilation	Arterial dilation	Calcium accumulation
Nitroglycerin (SL, rapid) Isosorbide mononitrate (oral)	Amlodipine Nifedipine	Ranolazine
Headache Unsafe drop in blood pressure with sildenafil	Antihypertensive and anti-anginal	Symptomatic medication only

Table 4.4: Anti-Anginal Medications
Summary table of the adjunct medications used to treat coronary artery disease.